Complete Summary

GUIDELINE TITLE

The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of diffuse large cell B-cell non-Hodgkin´s lymphoma: an evidence based review.

BIBLIOGRAPHIC SOURCE(S)

Hahn T, Wolff SN, Czuczman M, Fisher RI, Lazarus HM, Vose J, Warren L, Watt R, McCarthy PL Jr. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of diffuse large cell B-cell non-Hodgkin's lymphoma: an evidence-based review. Biol Blood Marrow Transplant 2001;7(6):308-31. [93 references] PubMed

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Diffuse large cell B-cell non-Hodgkin´s lymphoma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Hematology
Internal Medicine
Oncology
Pathology

INTENDED USERS

Health Plans
Managed Care Organizations
Patients
Physicians

GUIDELINE OBJECTIVE(S)

- To assemble and critically evaluate all of the evidence regarding the role of cytotoxic therapy with hematopoietic stem cell transplantation (SCT) in the therapy of diffuse large cell B-cell non-Hodgkin´s lymphoma (DLCL)
- To make treatment recommendations based on the available evidence
- To identify needed areas of research

TARGET POPULATION

Patients with diffuse large cell B-cell non-Hodgkin´s lymphoma who are candidates for hematopoietic stem cell transplantation

INTERVENTIONS AND PRACTICES CONSIDERED

Stem Cell Transplantation (SCT) Procedures

1. Double/tandem SCT
2. Myeloablative allogenic SCT
3. Nonmyeloablative allogenic SCT
4. Autologous bone marrow transplant (BMT)
5. Autologous peripheral blood SCT (PBSCT)
6. Purging
7. Stem cell mobilization method
8. Conditioning regimens
9. High-dose sequential therapy

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Event-free survival
- Disease-free survival
- Response/remission rates (complete/partial)
- Cost-effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Methodology

MEDLINE, the Web site of the National Library of Medicine, National Institutes of Health, was searched using the Medical Subject Heading (MeSH) term "Non-Hodgkin´s Lymphoma" limited to "Drug Therapy" or "Therapy." Search criteria were limited to English language, human trials, and publication dates between January 1980 and December 2000. In addition, a hand search was conducted of abstracts published by the American Society of Hematology in Blood, the American Society of Clinical Oncology in Journal of Clinical Oncology, and the European Group for Blood and Marrow Transplantation in Bone Marrow Transplantation for the meeting years 1997 to 2000; and for abstracts published in Annals of Oncology by the International Conference on Malignant Lymphoma for the 1999 meeting year.

Diffuse large cell B-cell lymphoma (DLCL) was defined as the Revised European-American Classification of Lymphoid Neoplasms (REAL) or World Health Organization (WHO) classification of diffuse large B-cell lymphoma; or International Working Formulation (IWF) subtypes F (diffuse mixed large and small cells), G (diffuse large cell), and H (diffuse large cell immunoblastic); or Kiel Classification centroblastic, centroblastic-centrocytic (diffuse), centrocytic (large), and immunoblastic B-cell; or Rappaport classification diffuse histiocytic B-cell lymphoma.

Inclusion/Exclusion Criteria

Published articles and abstracts studying stem cell transplantation (SCT) were included only if diffuse large cell B-cell non-Hodgkin´s lymphoma (DLCL) patients made up a minimum of 70% of the study population, unless results were stratified by histology subtype. The proportion of the study population with anaplastic large cell lymphoma is presented in the grading summary at the end of each major section but was not considered in calculating the 70% minimum required for inclusion. More than 250 abstracts and manuscripts that met the initial search criteria were ultimately excluded because they:

- did not study cytotoxic therapy with SCT
- studied therapy for relapse after SCT (studies of second transplantations were not excluded)
- did not assess overall survival (OS), disease-free survival (DFS), or event-free survival (EFS) (with the exception of studies of stem cell mobilization techniques)
- did not state the histologic subtypes (by IWF, Kiel, Rappaport, REAL, or WHO classifications)
- stated the histologic subtypes but included fewer than 70% DLCL patients or did not stratify the results by subtype
- studied human immunodeficiency virus (HIV)-associated lymphomas
- conducted a Phase I study (dose-escalation or dose-finding study)
- were reviews of the literature, editorials, case reports, or letters to the editor
- were abstracts subsequently published as manuscripts

A list of all excluded manuscripts and abstracts is available at the American Society for Blood and Marrow Transplantation Web site.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Grading the Quality of the Evidence

1

Evidence obtained from at least one properly randomized controlled trial

2-1

Evidence obtained from well-designated, controlled trials without randomization

2-2

Evidence obtained from well-designated, cohort or case-controlled analytic studies, preferably from more than one center or research group

2-3

Evidence obtained from multiple timed series with or without the intervention or from dramatic results in uncontrolled experiments

3

Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

4

Evidence inadequate owing to problems of methodology, e.g., sample size, length or comprehensiveness of follow-up, or conflict in evidence

Grading the Strength of the Evidence

1

Experimental therapy significantly better ($P < 0.05$)

2

Trend in favor of experimental therapy (P >0.05)

3

No apparent statistical effect

4

Trend favoring control group (P >0.05)

5

Control group significantly better (P <0.05)

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Study design, including sample size, patient selection criteria, duration of follow-up, and treatment plan were considered in evaluating the studies.

The published literature was graded on the quality of design (see Table 1 in the original guideline document) and the strength of the evidence (Table 2 in the original guideline document) in a systematic manner. Treatment recommendations were subsequently graded based on the quality and strength of the evidence (Table 3 in the original guideline document).

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading the Strength of the Treatment Recommendations

1

Effective treatment

2

Marginally effective treatment

3

Not an effective treatment (no statistical or clinical difference between therapies)

4

Inadequately evaluated treatment and recommended for comparative study

5

Inadequately evaluated treatment but not recommended for comparative study

COST ANALYSIS

Only one cost-effectiveness study has been conducted and evidence is insufficient. The study collected economic data comparing the costs associated with autologous bone marrow transplant (BMT) with the costs of standard chemotherapy. The mean costs associated with standard chemotherapy in the treatment period were significantly less than those in the BMT group (US $3,118 versus US $34,447; P <.01), but the average costs in the 2-year follow-up period were not significantly different between the groups (standard chemotherapy, US $12,436 versus BMT, US $15,837; P = NS). A comparison of long-term costs in a follow-up period of 8 years found higher but not statistically significant costs associated with BMT (US $56,512) compared to standard chemotherapy (US $20,397). The discounted life years (LYs) and quality-adjusted life years (QALYs) for BMT (LYs, 4.49; QALYs, 3.84) were lower than for standard chemotherapy (LYs, 5.04; QALYs, 4.33).

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The American Society for Blood and Marrow Transplantation (ASBMT) grades its recommendations (1–5) and the quality of the supporting evidence (1–4). The definitions of these grades can be found at the end of the "Major Recommendations" field.

Treatment Recommendations by Disease Response and International Prognostic Index (IPI) Risk* (Where Available)[a]

Indication for SCT in:	Treatment Recommendation[b]	Level of Evidence[c]	References[d]	Comments
First chemotherapy-sensitive relapse	1	1	Philip, Chauvin, Armitage et al., 1991; Philip, Chauvin, Bron et al., 1991; Philip et al., 1995; Blay et al., 1998	
Chemotherapy-resistant relapse/primary refractory disease	4	2	Saez et al., 1994; Mills et al., 1995; Stiff et al., 1998; Santini et al., 1999; Wheeler et al., 1993; Gribben et al., 1989; Gulati et al., 1992; Philip et al., 1987; Caballero et al., 1999; Horning et al., 1994; Sehn et al., 1998; Popat et al., 1998; Kewalramani et al., 2000	
First complete remission in patients with L/I-L IPI risk	3	1	Haioun et al., 1994	Based on results from the original analysis with short follow-up
First complete remission in patients with H/I-H IPI risk	1[e]	2	Haioun et al., 1994, 1997; Haioun, Lepage et al., 2000	Haioun et al. (1997 & 2000) show a benefit for SCT based on a retrospective unplanned subset analysis in the high-risk patients only. Haioun et al. (1994) demonstrates no benefit based on all randomized patients with short

Indication for SCT in:	Treatment Recommendation[b]	Level of Evidence[c]	References[d]	Comments
				follow-up.
First partial remission after full-course induction therapy	4	NA		
After abbreviated induction therapy (<6 cycles of CHOP or <12 cycles of MACOP-B or VACOP-B)	3[e]	1	Verdonck et al., 1995; Uyl-de Groot et al., 1995; Martelli et al., 1999; Reyes et al., 1997; Intragumtornchai et al., 1999	Verdonck et al. (1995) used a unique definition of partial response/remission (PR); Martelli et al. (1999) is still accruing patients; Reyes et al. (1997) significantly favors the standard chemotherapy arm, however included <70% DLCL.
As high-dose sequential therapy in untreated patients with I-H/H IPI risk	1	1	Gianni et al., 1997	
As high-dose sequential therapyin untreated patients with L/L-I IPI risk	4[e]	1	Milpied et al., 1999	Only 45% of the patients had low orlow-intermediate IPI risk; included 55% patients with high-intermediate or high IPI risk

*See Appendix B in original guideline document for definitions of IPI risk models.

[a]SCT indicates hematopoietic stem cell transplantation; L, low; I, intermediate; H, high; NA, no evidence available; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; MACOP-B, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin; VACOP-B, etoposide,

doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin; DLCL, diffuse large cell B-cell non-Hodgkin´s lymphoma.

[b]See below for definitions of recommendation ratings.

[c]See below for definitions of strength of evidence ratings. Levels 2-1 through 2-3 were condensed as Level 2 due to the heterogeneity of study designs represented by the references listed and for simplicity.

[d]The references listed represent the highest level of evidence used to make the treatment recommendation and are not inclusive of all evidence described in the review.

[e]Treatment recommendation is based on problems in methodology of the study(ies).

Treatment Recommendations for Transplantation Techniques*

Procedure Indicated	Treatment Recommendation[a]	Level of Evidence[b]	References[c]	Comments
Double/Tandem SCT	4	2	Haioun et al., 1998; Ballestrero et al., 1998; Clavio et al., 1999	Studies consisted of mixed population of untreated, relapsed, and refractory patients
Myeloablative allogeneic SCT	4	2	van Biesien et al., 1996; Dhedin et al., 1999	
Nonmyeloablative allogeneic SCT	4	NA		
Autologous BMT	1	1	Philip, Chauvin, Armitage et al., 1991; Philip, Chauvin, Bron et al., 1991; Philip	

Procedure Indicated	Treatment Recommendation[a]	Level of Evidence[b]	References[c]	Comments
			et al., 1995; Blay et al., 1998; Haioun et al., 1994, 1997; Haioun, Lepage et al., 2000	
Autologous PBSCT	1	3		
Purging	4	2	Weisdorf et al., 1991	
Stem cell mobilization method	4	2	Petit et al., 1999; Donato et al., 1999; Haioun, Van Hoof et al., 2000	
Conditioning regimens	4	NA		
As high-dose sequential therapy in patients with I-H/H IPI risk	1	1	Gianni et al., 1997	
As high-dose sequential therapy in patients with L/L-I IPI risk	4	1	Milpied et al., 1999	Only 45% of the patients had low or low-intermediate IPI risk; included 55% patients with high-intermediate or high IPI

Procedure Indicated	Treatment Recommendation[a]	Level of Evidence[b]	References[c]	Comments
				risk

*SCT indicates hematopoietic stem cell transplantation; NA, no evidence available; BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; L, low; I, intermediate; H, high; IPI, International Prognostic Index.

[a]See below for definitions of recommendation ratings.

[b]See below for definitions of strength of evidence ratings. Levels 2-1 through 2-3 were condensed as Level 2 due to the heterogeneity of study designs represented by the references listed and for simplicity.

[c]The references listed represent the highest level of evidence used to make the treatment recommendation and are not inclusive of all evidence described in the review.

Definitions:

Rating Scheme for Strength of Evidence

1

Evidence obtained from at least one properly randomized controlled trial

2-1

Evidence obtained from well-designated, controlled trials without randomization

2-2

Evidence obtained from well-designated, cohort or case-controlled analytic studies, preferably from more than one center or research group

2-3

Evidence obtained from multiple timed series with or without the intervention or from dramatic results in uncontrolled experiments

3

Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

4

Evidence inadequate owing to problems of methodology, e.g., sample size, length or comprehensiveness of follow-up, or conflict in evidence

Rating Scheme for Strength of Recommendations

1

Effective treatment

2

Marginally effective treatment

3

Not an effective treatment (no statistical or clinical difference between therapies)

4

Inadequately evaluated treatment and recommended for comparative study

5

Inadequately evaluated treatment but not recommended for comparative study

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Evidence-based and cost-effective use of stem cell transplantation in the treatment of patients with diffuse large cell B-cell non-Hodgkin´s lymphoma
- Improved survival rates following stem cell transplantation

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Study Limitations

There are limitations to any evidence-based review of the published medical literature. The criteria for this review included reliance on only published data, specifically peer reviewed articles published since 1980, and abstracts from the 3 most recent years of annual meetings where studies of stem cell transplantation (SCT) and/or non-Hodgkin´s lymphoma (NHL) are presented. Unpublished data, which were not included in this review, often represent "negative" findings and usually do not undergo peer review. We included studies presented in abstract form for the purpose of identifying "negative" clinical trials and preliminary analyses of "positive" clinical trials, with the understanding and acknowledgment that abstracts do not undergo rigorous peer review and do not contain the same level of study detail presented in published articles.

Another limitation of this review is its reliance on published data rather than on individual patient data. The stated goal of the review was to present evidence for making recommendations regarding the role of SCT in the treatment of diffuse large cell B-cell non-Hodgkin´s lymphoma (DLCL). Time and financial constraints made it impractical to obtain data on individual patients from the large number of clinical trials included in this review. Although it was not the objective of this review to perform an extensive meta-analysis of the data, such an analysis is warranted to further clarify the results of studies and address unanswered questions.

Many studies were excluded from this analysis because they did not meet the stringent inclusion criteria for this review, namely the identification of histologic subtypes and the inclusion of at least 70% of patients having DLCL subtype.

Most of the excluded studies addressed transplantation technologies (e.g., autologous versus allogeneic donors, peripheral blood SCT [PBSCT] versus bone marrow transplantation [BMT], purged versus unpurged BMT), rather than comparisons between SCT and standard chemotherapy. These included several randomized trials and registry reports comparing autologous and allogeneic BMT for lymphoma patients and PBSCT versus BMT in NHL patients. These and other studies could have provided much needed evidence in these areas but they could not be included because it was not stated whether the evidence was applicable to DLCL patients.

It should also be noted that inclusion criteria were not based on the availability of patient International Prognostic Index (IPI) scores because most of the phase III trials were already accruing patients or had been analyzed prior to publication of the IPI project. It is acknowledged that significant differences in prognosis and outcomes by IPI have been identified, and applicability of results may be problematic if the IPI risk categories of patients are not stated.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Hahn T, Wolff SN, Czuczman M, Fisher RI, Lazarus HM, Vose J, Warren L, Watt R, McCarthy PL Jr. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of diffuse large cell B-cell non-Hodgkin's lymphoma: an evidence-based review. Biol Blood Marrow Transplant 2001;7(6):308-31. [93 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2001 Apr

GUIDELINE DEVELOPER(S)

American Society for Blood and Marrow Transplantation - Professional Association

SOURCE(S) OF FUNDING

American Society for Blood and Marrow Transplantation

GUIDELINE COMMITTEE

DLCL Expert Panel Steering Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: Theresa Hahn, Roswell Park Cancer Institute, Buffalo, New York; Steven N. Wolff, Vanderbilt University, Nashville, Tennessee; Myron Czuczman, Roswell Park Cancer Institute, Buffalo, New York; Richard I. Fisher, Cardinal Bernardin Cancer Center, Loyola University, Chicago, Illinois; Hillard M. Lazarus, Comprehensive Cancer Center, University Hospitals of Cleveland, Case Western Reserve University, Cleveland, Ohio; Julie Vose, University of Nebraska Medical Center, Omaha, Nebraska; Lisa Warren, Cure Fjor Lymphoma Foundation, New York, New York; Richard Watt, United Resource Networks, Minneapolis, Minnesota; Philip L. McCarthy, Jr., Roswell Park Cancer Institute, Buffalo, New York

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Society for Blood and Marrow Transplantation Web site.

Print copies: Available from Theresa Hahn, PhD, Roswell Park Cancer Institute, Department of Medicine, Elm & Carlton Sts, Buffalo, NY 14263; e-mail: Theresa.Hahn@RoswellPark.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Position statement of the American Society for Blood and Marrow Transplantation: the role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of diffuse large cell B-cell non-Hodgkin's lymphoma. Arlington Heights (IL): American Society for Blood and Marrow Transplantation; 2003. 2 p.

Electronic copies: Available in Portable Document Format (PDF) from the American Society for Blood and Marrow Transplantation Web site.

Print copies: Available from Theresa Hahn, PhD, Roswell Park Cancer Institute, Department of Medicine, Elm & Carlton Sts, Buffalo, NY 14263; e-mail: Theresa.Hahn@RoswellPark.org.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on June 14, 2004. The information was verified by the guideline developer on June 30, 2004.

COPYRIGHT STATEMENT

Date Modified: 11/15/2004